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TITLE: Neural and Behavioral Sequelae of Blast-Related Traumatic Brain Injury

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14. ABSTRACT

Traumatic brain injuries (TBI) are a common occurrence from roadside blasts of improvised explosive devices (IEDs). In this cross-sectional study, we applied neurobehavioral testing and advanced MRI techniques [task-activated functional MRI (fMRI) and diffusion tensor imaging (DTI)] to gain a comprehensive understanding of the neural changes underlying blast-related mild TBI (MTBI). We accomplished this goal by conducting advanced neuroimaging (task-activated fMRI and DTI fiber tracking) and neurobehavioral testing (computerized assessment and standard neuropsychological testing) on 60 chronic trauma patients: 15 military MTBI patients who had blast injuries, 15 civilian MTBI patients with mechanical closed head injuries, 15 military and 15 civilian patients with orthopedic injuries. Key findings on the stop signal fMRI task include a distinct pattern of brain activation in the military blast MTBI group which differed from the civilian MTBI group on failed inhibition trials. On the Sternberg working memory task, fMRI findings show that increases in brain activation with memory load are reduced in specific brain regions of the military blast MTBI group, also suggesting that the chronic effects of blast MTBI differ from mechanical MTBI in civilians. We completed recruitment of subjects, scoring and entering of outcome data, and continue imaging data analysis.

15. SUBJECT TERMS
Blast-related traumatic brain injury (TBI), fMRI, DTI, cognition

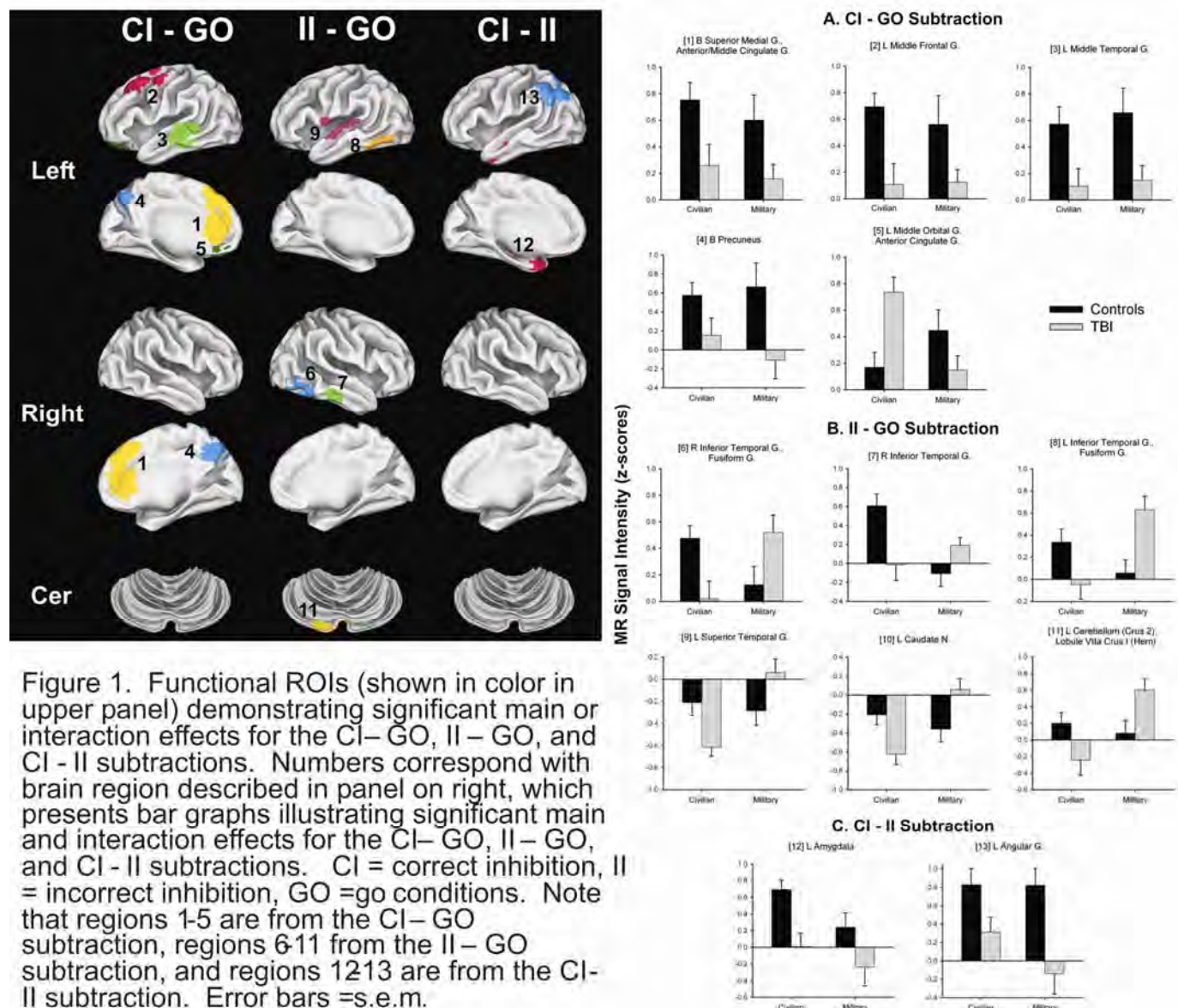| **16. SECURITY CLASSIFICATION OF:**			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON** USAMRMC
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INTRODUCTION

Traumatic brain injuries (TBI) are a common occurrence from roadside blasts of improvised explosive devices (IEDs). Like civilian TBI, blast-related TBI can result from mechanical forces in which objects in motion strike the head or the head is forcefully put into motion and strikes an object. TBI from exposure to an explosive blast may also result from a third cause: barotrauma. Blasts produce wave-induced changes in atmospheric pressure, which in turn produce characteristic injuries to vulnerable bodily regions at air-fluid interfaces, such as the middle ear. It is unknown whether the neural and cognitive sequelae of blast-related TBI differ from those resulting from mechanically-induced TBI commonly observed in civilian accidents. Understanding the potentially unique sequelae of blast-related TBI is critical for accurate diagnosis and designing effective pharmacological and neurorehabilitation interventions.

In the proposed cross-sectional study, we aim to apply neurobehavioral testing and advanced MRI techniques [task-activated functional MRI (fMRI) and diffusion tensor imaging (DTI)] to gain a comprehensive understanding of the neural changes underlying blast-related MTBI. This will be accomplished by comparing neurobehavioral and neuroimaging findings obtained from military personnel who have experienced a blast injury with those obtained from civilians who have experienced TBI from motor vehicle accidents and from military and civilian control participants with orthopedic injuries. We will accomplish this goal by conducting advanced neuroimaging (task-activated fMRI and DTI fiber tracking) and neurobehavioral testing (computerized assessment and standard neuropsychological testing) on 60 chronic trauma patients: 15 military MTBI patients who have experienced blast injuries, 15 civilian MTBI patients with mechanical closed head injuries,15 military and 15 civilian patients with orthopedic injuries.

BODY

Study 1. Our first fMRI analysis involved the Stop Signal Task, results of which will be published in the *Journal of Neurotrauma* (preprint located in the Appendix). To summarize results of this study (see Fig. 1 below), we found common and distinct patterns of brain activation in blast (military) versus mechanical (civilian) TBI. During correct inhibitions, both TBI groups demonstrated decreased activation in the default mode network (DMN). In contrast, during failed inhibition trials, blast TBI exhibited hyperactivation and mechanical TBI produced hypoactivation. These divergent brain activation patterns were independent of self-reported complaints, including PTSD.   The identification of an imaging test that is specifically sensitive to blast TBI in humans raises numerous clinical possibilities. It is conceivable that our brain activation patterns in response to an inhibitory control task could be used as a basis for the diagnosis of blast TBI in the clinical setting. The efficacy of potential treatments for the sequelae of blast TBI could also be measured with this imaging biomarker. This is critical since neuropsychological testing is relatively insensitive to the chronic effects of mild to moderate blast TBI. Finally, these findings suggest possibilities for developing an animal model for testing the effects of blast trauma on neural function based on inhibitory control testing.

Figure 1. Functional ROIs (shown in color in upper panel) demonstrating significant main or interaction effects for the CI– GO, II – GO, and CI - II subtractions. Numbers correspond with brain region described in panel on right, which presents bar graphs illustrating significant main and interaction effects for the CI– GO, II – GO, and CI - II subtractions. CI = correct inhibition, II = incorrect inhibition, GO =go conditions. Note that regions 1-5 are from the CI– GO subtraction, regions 6-11 from the II – GO subtraction, and regions 12-13 are from the CI-II subtraction. Error bars =s.e.m.

Study 2. We have completed the fMRI analysis of the Sternberg Working Memory Task. Results will be submitted for publication in late September, 2013. This study involved 100 chronic trauma patients (derived from the Cleveland and Houston sites): 25 military MTBI patients who have experienced blast injuries, 25 civilian MTBI patients with mechanical closed head injuries, 25 military controls, and 25 civilian patients with orthopedic injuries. The Sternberg working memory task consisted of a total of 72 trials distributed over three imaging runs. A schematic of the task is presented in the upper panel of Figure 2. During the Encode phase, participants were asked to commit to memory 1, 3, or 5 consonants over an 1800 msec. interval. The number of encoded items constituted the working memory load or set size with 24 trials for each set size; trials were pseudo-randomized across set size. To maintain the same amount of visual information across the set sizes, asterisks were used to replace letters for set sizes 1 and 3. Immediately following the Encode phase, participants viewed a centrally fixated "+" for 4300 msec (Maintenance phase). This was followed by the Response phase, in which a single probe letter appeared on the screen for 2800 msec. On 50% of trials, the probe letter matched one of the items presented during the Encode phase.   Participants were instructed to respond with their right index finger keypress if the probe letter matched a letter in the Encode stimulus set or their right middle finger if the target did not match. The inter-trial interval consisted of centrally fixated "+" that varied in duration from 3830 to 14,330 msec to introduce "jitter" into the time series for the analysis of this event-related fMRI task.
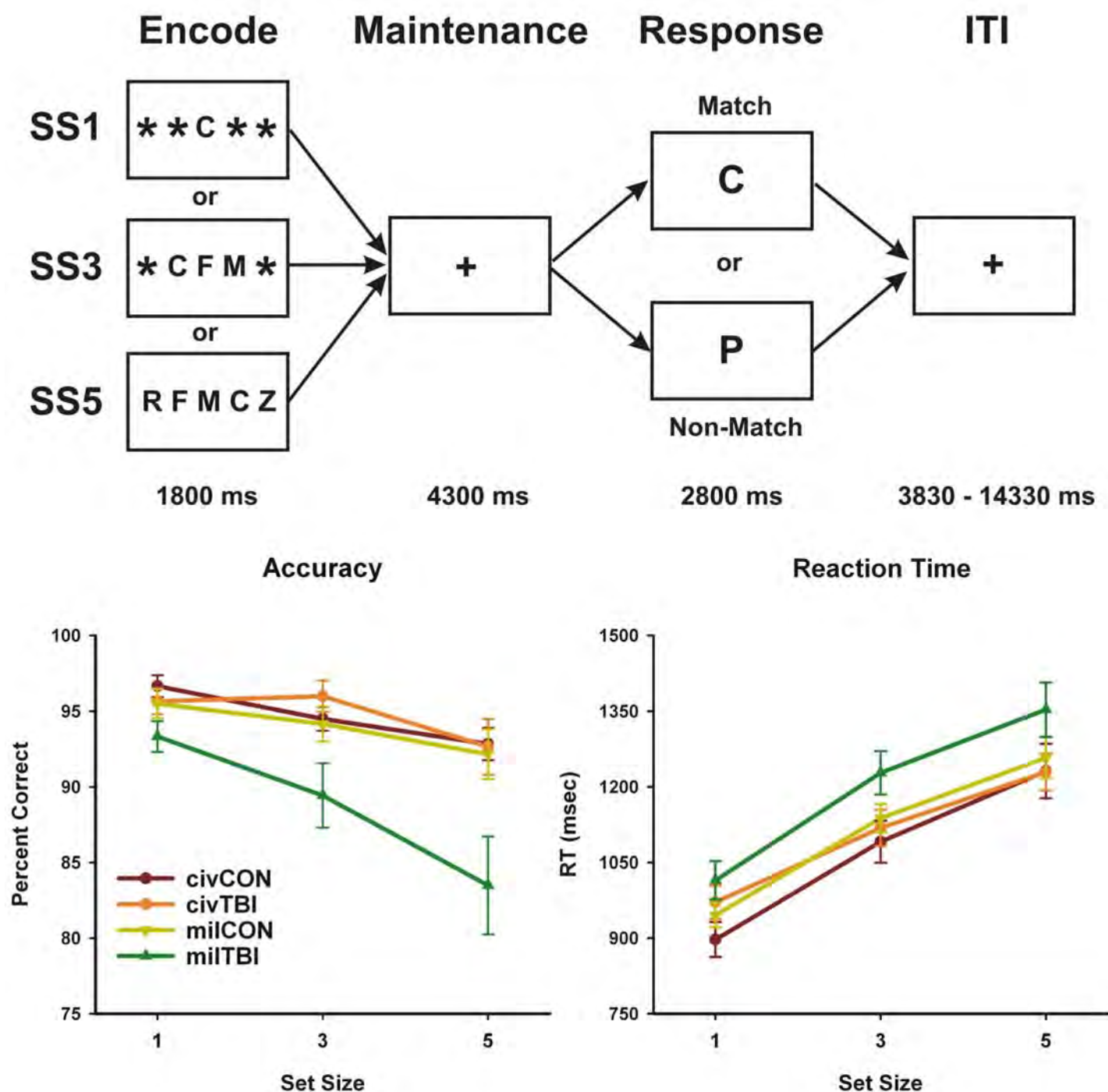
Figure 2. (upper panel) Schematic of Sternberg Working Memory Task (see description above). (lower panel) Accuracy and reaction time results as a function of set size (working memory load) for the 4 participant groups.

Behavioral performance on the Sternberg task was measured in terms of accuracy and reaction time (see lower panel of Fig. 2). Overall accuracy, collapsed across set sizes, had a significant group effect, with the milTBI group showing the lowest accuracy rates. At the most difficult working memory condition (SS5), the milTBI group was less accurate than the other three groups (milCON, civTBI, civCON) (see Fig 2). Despite these group differences, all four groups performed well above chance (50%). Analysis of reaction time was conducted in three different ways. First, the average reaction time was calculated across all set sizes. There were no significant differences between the means of overall reaction time between the groups. Second, the reaction times were analyzed for each individual set size. At SS1, the TBI groups (civTBI and milTBI) were

significantly slower than the control groups (civCON and milCON). Finally, a linear regression was fit for each subject, with reaction time as the dependent variable and set size as the independent variable. From this regression, the slope and intercept were extracted and compared using a 2x2 ANOVA. The average intercept of the TBI groups was significantly greater than the average intercept of the control groups. No significant group differences were observed for slope.

The fMRI analysis involved the derivation of functional ROI (fROI) from a disjunction mask (details of the method are contained in the Stop Signal preprint (see Appendix). The disjunction analysis identified 25 Encode fROIs that demonstrated differential activation based on set size. All fROIs were analyzed for set size by group effects using a 3x2x2 ANOVA. False discovery rate (FDR) was used to control for multiple comparisons. None of the regions had a significant interaction effect between military service (mil vs. civ) and working memory load. Seven brain regions demonstrated significant interaction effects of working memory load and the presence/absence of a TBI (see Fig. 3 below). These included 3 cortical regions (left insula/inferior frontal gyrus, bilateral middle orbital frontal gyrus, and right middle occipital gyrus), 3 subcortical regions (right head/body of the caudate, right tail of the caudate, and left caudate/putamen/pallidum), and the cerebellar vermis. In 5 regions (left insula/inferior frontal gyrus, right head/body of the caudate, right tail of the caudate, left caudate/putamen/pallidum, and cerebellar vermis), the two non-injured control groups demonstrated a monotonic increase in fMRI signal intensity with increasing load; the two TBI groups failed to demonstrate this monotonic increase (Fig. 3). In 2 regions (bilateral middle orbital frontal gyrus, and right middle occipital gyrus), the two control groups demonstrated a decrease in activation ("deactivation") at SS3; in contrast, the TBI group did not demonstrate deactivation at SS3 (Fig. 3). Two regions demonstrated 3-way interactions: right tail of the caudate and right head/body of the caudate (see row 3, middle and rightmost graphs in Fig. 3). In both of these ROIs, activation in the milTBI group did not change with working memory load, whereas the three other groups demonstrated a monotonic increase associated with working memory load.

Several conclusions may be drawn from this study: 1) working memory task performance is impaired in milTBI participants more than 50 months post-injury; 2) both military and civilian TBI participants demonstrate an abnormal under-activation of cortical and subcortical brain regions in response to increasing working memory load; 3) blast and mechanical TBI can be differentiated based on activation of the right caudate nucleus, suggesting that this subcortical structure is particularly vulnerable to the effects of blast exposure; 4) these findings did not change when results from PTSD and other self-report scales were used as covariates, indicating that the main conclusions are due to the long-term sequelae of TBI rather than the effects of a mental health disorder.

Study 3. We have just begun an analysis of the DTI data. DTI data were first processed using the Tract-Based Spatial Statistics (TBSS) program found in FSL 4.0 image processing software (http://www.fmrib.ox.ac.uk/fsl/tbss/index.html) to create a mean white matter skeleton. Specifically, all FA images were aligned to a cubic 1 mm standard space and the FMRIB58 standard image. FA images were averaged and a skeleton created with an FA threshold of 0.2 representing tracts common to all participants. This method of "thinning" each white matter tract perpendicular to the tract and thresholding FA helps eliminate the threat of partial volume effects and areas of high inter-subject variability. Each participant's maximum FA value from the nearest relevant tract center was assigned to the corresponding skeleton voxel, which corrects for residual misalignments after nonlinear registration. Following the creation of the FA skeleton, white matter tracts of interest were created using the ICBM DTI-81 white matter atlas.[24] The ICBM DTI-81 atlas is a hand-segmented white matter parcellation map based on the probabilistic tensor maps of 81 healthy subjects. The atlas consists of 48 white matter tracts based on acceptable levels of intra- and inter-rater reliability. The atlas includes only portions of white matter tracts that are reproducible based on tractography studies. Using the Analysis of Functional Neuroimages (AFNI) software package, the TBSS-derived FA skeleton was overlaid onto the ICBM DTI-81 atlas. From this conjunction map, mean FA, MD, DA, and DR values were calculated for each subject for each white matter tract of interest. Two-way ANOVAs were performed to assess group differences for each white matter tract and each DTI parameter (FA, MD, DA, DR). The false discovery rate (FDR) method was performed separately for each DTI parameter to control for multiple comparisons. Post hoc

analyses were conducted using Tukey HSD. Preliminary results (Fig. 4) suggest differences in DR between blast and mechanical TBI in the right and left posterior internal capsule. Blast TBI results in an increase in DR relative to the military controls, whereas the DR of participants with mechanical TBI do not differ from the DR of civilian controls.
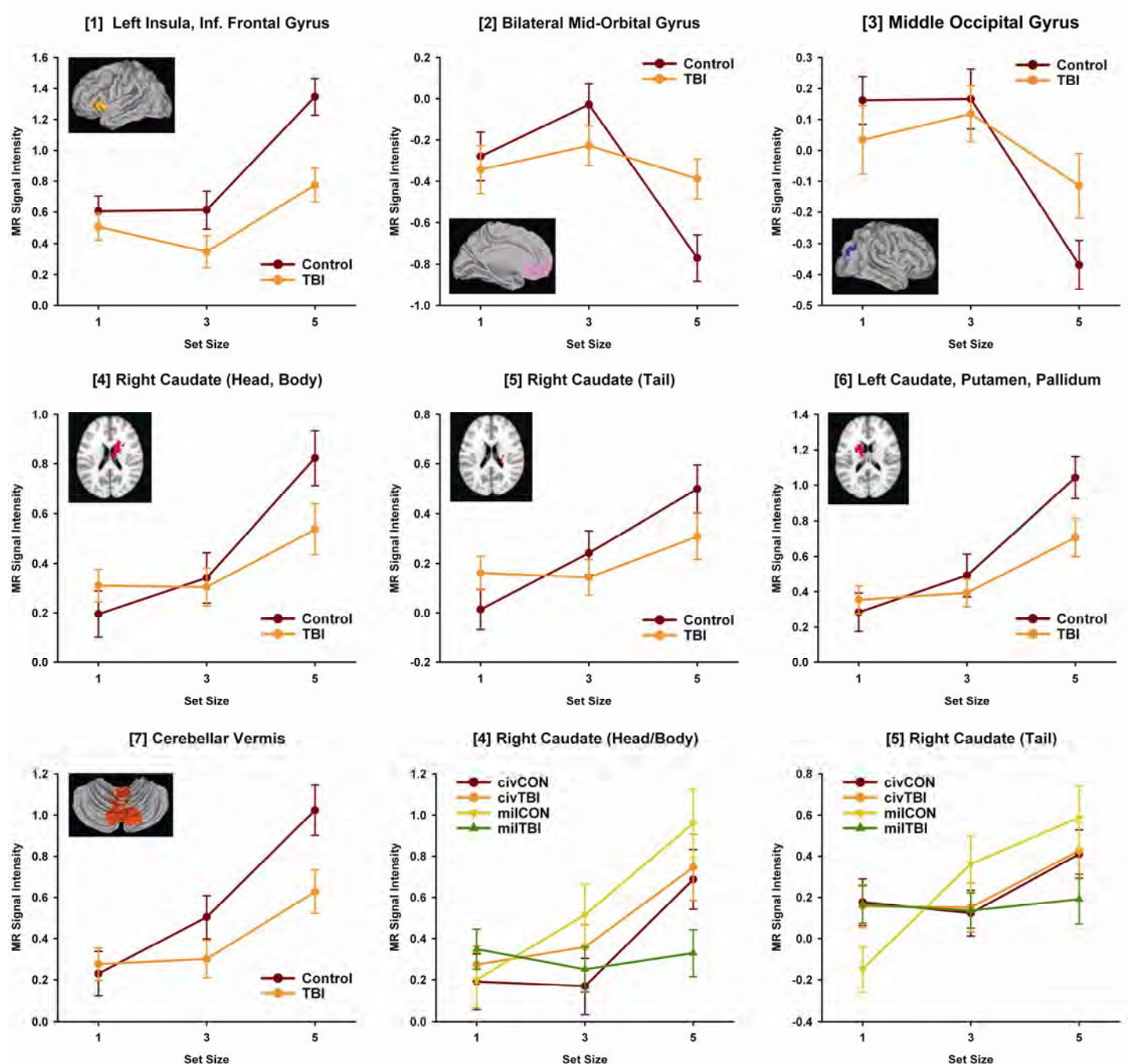

Figure 3. Brain regions demonstrating significant 2-way (TBI/CON x memory load) interactions (regions 1-7) and 3-way (TBI/CON x mil/civ x memory load) interactions (regions 4 and 5).
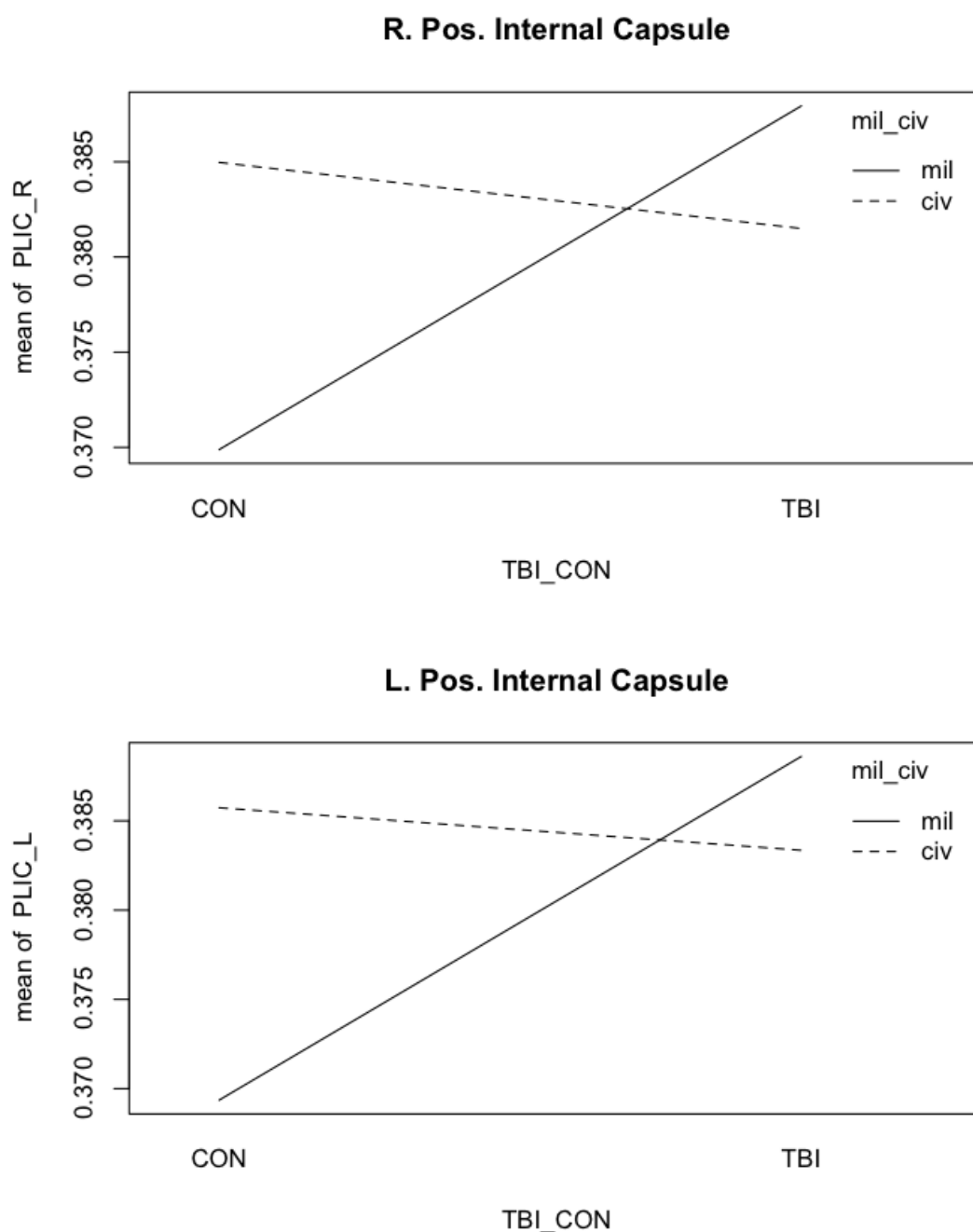
R. Pos. Internal Capsule

L. Pos. Internal Capsule

Figure 4. Significant interaction of TBI/CON and mil/civ related to radial diffusivity in the right and left posterior internal capsule.

KEY RESEARCH ACCOMPLISHMENTS

The key accomplishments at the completion of the project in Cleveland, in collaboration with Houston, can be summarized as:

- Chronic effects of blast related mild traumatic brain injury (mTBI) in Veterans include reorganization of the brain's functional architecture for inhibitory control and working memory as reflected by a pattern of activation on the stop signal and Sternberg working memory tasks.
- In comparison with civilians who sustained mTBI by non-blast mechanisms such as motor vehicle crashes and sports, Veterans with chronic blast TBI exhibit increased brain activation on trials when they failed to

make a correct inhibitory response and a failure to demonstrate a monotonic increase in brain activation as working memory load increases.

- Functional magnetic resonance imaging findings during the stop signal and Sternberg tasks indicate a distinct pattern of brain activation which may have diagnostic implications pending replication.
- Preliminary analyses of DTI data suggest that blast-related mTBI, as opposed to mechanical mTBI, may be associated with an increase in radial diffusion involving the posterior internal capsule.

REPORTABLE OUTCOMES

The Houston and Cleveland groups have collaborated on submission of a manuscript reporting the results for the Stop Signal task, which will be published in the *Journal of Neurotrauma* (see Appendix).

We are very close to submitting an additional paper pertaining to results of the Sternberg working memory task.

Analyses continue on the DTI data and its relationship to the findings on task-activated fMRI.

In April, 2013, Dr. Levin and Dr. Rao submitted pre-application #130547 to CDMRP entitled "Violent Criminal Offenses by Veterans in Relation to Traumatic Brain Injury Sustained During Deployment: Brain Imaging, Behavior, and Genetics" The pre-application, which was not selected for a full proposal, proposed to use the Stop Signal task, directly building on accomplishments of this CDMRP grant.

In September, 2013, Dr. Rao will submit a pre-application to TATRC entitled "Advanced Neuroimaging of Chronic Traumatic Encephalopathy in Retired NFL Football Players." This pre-application plans to use the Stop Signal and Sternberg tasks and DTI, directly building on accomplishments of this CDMRP grant.

Presentations:

Deborah Warden Lectureship: Neurobehavioral Outcome of Blast Related Traumatic Brain Injury: Current findings, Implications for Clinical Services and Directions for Research. 5th Annual Defense and Veterans Traumatic Brain Injury Summit, National Harbor, MD, 2011

Chronic Outcome of TBI in Blast Brain Injury Subjects. National Neurotrauma Society Annual Meeting 2012, Phoenix, AZ

Diffusion Tensor Imaging: Co-morbidities, Complications, and Controversies. 8th Annual Blast Injury Conference, Organized by Polytrauma Program, Veterans Affairs Medical Center, December 14, 2011 Tampa, FL

Neural activation during response inhibition differentiates blast from mechanical causes of mild to moderate traumatic brain injury. Annual Meeting of the International Neuropsychological Society, February, 2013, Waikoloa, Hawaii.

Effects of Blast-Related mTBI on Neural Activation during Performance of a Working Memory Task. To be presented at the Annual Meeting of the International Neuropsychological Society, February, 2014, Seattle, Washington.

Cleveland Clinic personnel receiving pay from research effort:

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CONCLUSION

Blast related mTBI in Veterans appears to be associated with distinctive patterns of brain activation on the Stop Signal Task, a measure of response inhibition, and on the Sternberg Task, a measure of working memory. These patterns, which differs from Veterans who did not sustain TBI during deployment and from civilians who sustain non-blast mTBI, may have clinical application pending replication.

REFERENCES

Article:

Fischer, B.L., Parsons, M., Durgerian, S., Reece, C., Mourany, L., Lowe, M.J., Beall, E.B., Koenig, K.A., Jones, S.E., Newsome, M.R., Scheibel, R.S., Wilde, E.A., Troyanskaya, M., Merkley, T.L., Walker, M., Levin, H.S., & Rao, S.M. (in press). Neural activation during response inhibition differentiates blast from mechanical causes of mild to moderate traumatic brain injury. *Journal of Neurotrauma.*

Abstract:

Parsons M, Durgerian S, Reece C, Mourany L, Bura A, Lowe M, Beall E, Koenig K, Scheibel R, Newsome M, Troyanskaya M, Levin H & Rao S. (2013). Abnormal brain activation during inhibitory control in blast-related mild TBI. *Journal of the International Neuropsychological Society, 19 (Suppl. 1),* 13.

APPENDICES

The Stop Signal fMRI manuscript, accepted for publication by the *Journal of Neurotrauma,* is appended to the end of this report.

SUPPORTING DATA

None at this time

Journal of Neurotrauma

Neural Activation during Response Inhibition Differentiates Blast from Mechanical Causes of Mild to Moderate Traumatic Brain Injury

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Manuscripts

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Neural Activation during Response Inhibition Differentiates Blast from Mechanical Causes of Mild to Moderate Traumatic Brain Injury

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Abstract

Military personnel involved in Operations Enduring Freedom and Iraqi Freedom (OEF/OIF) commonly experience blast induced mild to moderate traumatic brain injury (TBI). In this study, we used task-activated functional MRI (fMRI) to determine if blast-related TBI has a differential impact on brain activation in comparison to TBI caused primarily by mechanical forces in civilian settings. Four groups participated: (1) blast-related military TBI (milTBI; n=21); (2) military controls (milCON; n=22); (3) non-blast civilian TBI (civTBI; n=21); and (4) civilian controls (civCON; n=23) with orthopedic injuries. Mild to moderate TBI (MTBI) occurred 1 to 6 years prior to enrollment. Participants completed the Stop Signal Task (SST), a measure of inhibitory control, while undergoing fMRI. Brain activation was evaluated with 2 [mil, civ] X 2 [TBI, CON] ANOVAs, corrected for multiple comparisons. During correct inhibitions, fMRI activation was lower in the TBI than CON subjects in regions commonly associated with inhibitory control and the default mode network. In contrast, inhibitory failures showed significant interaction effects in the bilateral inferior temporal, left superior temporal, caudate, and cerebellar regions. Specifically, the milTBI group demonstrated more activation than the milCON group when failing to inhibit; in contrast, the civTBI group exhibited less activation than the civCON group. Covariance analyses controlling for the effects of education and self-reported psychological symptoms did not alter the brain activation findings. These results indicate that the chronic effects of TBI are associated with abnormal brain activation during successful response inhibition. During failed inhibition, the pattern of activation distinguished military from civilian TBI, suggesting that blast-related TBI has a unique effect on brain function that can be distinguished from TBI resulting from mechanical forces associated with sports or motor vehicle accidents. The implications of these findings for diagnosis and treatment of TBI are discussed.

Keywords: Traumatic brain injury, fMRI, brain activation, inhibitory control, blast-related TBI, mechanical TBI

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Introduction

Traumatic brain injury (TBI) is common in military personnel involved in the Operations Iraqi Freedom and Enduring Freedom (OIF/OEF) conflicts.[1-4] Epidemiological studies suggest that the prevalence of TBI ranges from 15-28%[1, 5, 6] with a majority of these TBIs (50-79%) resulting from blasts caused by improvised explosive devices.[1, 7, 8]

Blast induced TBI may involve different mechanisms than TBI occurring in civilian settings. Whereas most head trauma in civilians results from mechanical processes such as acceleration/deceleration or rotational forces[9], blast induced TBI is thought to result from rapid changes in atmospheric pressure producing over- and/or under-pressurization. Blast-related damage is thought to occur within internal organs, particularly at air-fluid junctures.[10] Hypothesized mechanisms of blast induced brain injury include transcranial or intravascular propagation of blast energy, as well as indirect transmission via cerebrospinal fluid through the foramen magnum.[2] In addition to injury caused by these primary blast forces, damage may result from mechanical forces resulting from displaced projectiles such as bricks, nails, etc. (secondary blast forces). A third form of blast injury occurs following the structural disintegration of buildings and vehicles leading to crush injuries or of individuals being slammed into hard surfaces (tertiary blast forces). Thus, military personnel frequently experience both the pressurization effects of blast in combination with mechanical forces (blast + mechanical), and may sustain multiple such injuries over the course of their deployment.[11]

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Animal models have revealed numerous pathological, biochemical and behavioral changes as a result of blast exposure.[3] Among the blast sequellae noted in animals are diffuse axonal injury[12], sub-arachnoid and parenchymal bleeding[13], increases in intracranial pressure [14], evidence of hippocampal neurodegeneration, phosphorylated tau protein and astrocytosis[15], vasospasm and white matter degeneration[16], increased levels of mortality, brain edema[17], and downregulation of genes associated with hippocampal neurogenesis.[18] Despite these advances in knowledge from animal models, there remains controversy as to whether the clinical and neuropathological features of blast and mechanical TBI are the result of a unitary mechanism of injury[15] or the result of unique and distinguishable injury parameters.[16, 17]

Attempts to distinguish blast-related from mechanical TBI in humans have met with mixed results. Mild to moderate TBI's typically do not have macroscopic abnormalities on structural MRI. Although we have observed subtle differences in cognitive performance in blast-related TBI[19], the cognitive deficits observed in the acute and subacute stage of mild to moderate TBI typically resolve in the chronic stage. Belanger et al.[20] have suggested that any differences between blast-related and mechanical TBI are likely the result of increased levels of psychological distress in blast-related TBI rather than any unique differences in brain pathology. An alternative strategy for differentiating blast-related from mechanical TBI is to identify unique neural signatures in brain activation patterns using fMRI. Several fMRI studies have identified anomalous brain activation patterns in mechanical[21, 22] and blast-related[23] TBI compared to non-TBI control groups, but none to date has directly compared blast-related and mechanical TBI.

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In this task-activated fMRI study, we compared blast-related and mechanical TBI using a measure of response inhibition, the Stop Signal Task (SST). Response inhibition involves the ability to stop or suspend an intended or initiated action.[24] Problems with inhibitory control are common in mild to moderate TBI.[25, 26] To our knowledge, only one fMRI study has evaluated inhibitory control in blast-related TBI. Matthews et al.[27] compared OEF/OIF Veterans who had experienced blast-related concussion with either loss of consciousness (LOC) or alteration of consciousness (AOC) using the SST. While the two groups did not differ in task performance, TBI individuals with LOC demonstrated significantly reduced activation in the left ventromedial prefrontal cortex than those with AOC on "easy" trials. There were no significant group differences in activation on "difficult" trials. The study did not compare blast-related TBI to civilian TBI nor to healthy controls.

The present fMRI study, therefore, was designed to identify possible differences between blast-related and mechanical TBI in the brain activation patterns evoked by an inhibitory control task (SST). Our focus was on the long term neural sequelae, with our TBI participants at least 12 months post injury. In addition to the military blast-related TBI and civilian non-blast TBI participant groups, we recruited two healthy control groups: a military group with combat exposure during the OEF/OIF conflict and a civilian group who experienced an orthopedic injury. We hypothesized that brain activation patterns would discriminate TBI and healthy control groups and, most importantly for this study, blast-related and mechanical TBI groups.

Materials and Methods

Participants. All procedures and recruitment strategies were reviewed and

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approved by the institutional review boards of the Cleveland Clinic, Stokes Veterans

Affairs Medical Center-Cleveland (VAMC), and the U.S. Department of Defense;

participants provided written informed consent. Four groups of participants were

enrolled: (1) OEF/OIF Veterans with blast-related MTBI (*milTBI*), (2) deployed OEF/OIF

Veterans, who never experienced blast and/or head injury, served as milTBI controls

(*milCON*), (3) civilians with MTBI (*civTBI*) due to sports or motor vehicle accidents, and

(4) civilians with orthopedic injuries served as civTBI controls (*civCON*).

Veterans were recruited primarily through letters mailed out from the Cleveland

VAMC. The pool for recruitment included all OEF/OIF Veterans who had registered for

VAMC-related services (not restricted to head injury). Letters were sent to those

individuals describing the study and inviting them to participate if they suffered a head

injury (milTBI) or served but did not suffer a head injury (milCON). Veterans were also

recruited via referral to the study from a VAMC physician and through advertisements

posted at local colleges and in newspapers. Civilian participants were recruited

primarily through informational mailings sent from their treating physician at the

Cleveland Clinic.

Potential participants initially underwent telephone screening to determine

eligibility. Those participants meeting inclusion/exclusion criteria (see below) were

invited to undergo a neuroimaging examination at the Cleveland Clinic. Attempts were

made to match the four groups with regard to age, gender, education, and, in the case

of TBI participants, time since injury. Specific details of the inclusion/exclusion criteria

for each group are as follows:

milTBI participants sustained a blast-related TBI during deployment between 1

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and 6 years prior to enrollment. In order to be considered eligible for inclusion, prospective participants must have experienced a blast induced injury that resulted in LOC, AOC, or a period of post-traumatic amnesia (PTA), following the event. This was assessed via self-report, but with trained interviewers who probed/clarified responses in an attempt to obtain the most accurate information possible (e.g., distinguishing true AOC from "fog of war"). If there was a LOC, it must not have exceeded 24 hours in duration and, if PTA occurred, it must not have exceeded 7 days. Furthermore, milTBI participants had no observable intracranial injury on computer tomography (CT) scan (if available) and their Glasgow Coma Scale (GCS) score was between 9 and 15 (if available). For those participants with multiple head injuries, the most severe served as the "index injury" for purposes of estimating time since injury.

milCON served in active OEF/OIF duty within the prior 6 years but had no history of brain injury, primary blast exposure, or LOC during their deployment. This group controlled for the nonspecific emotional distress associated with combat. These participants had no history of TBI either pre- or post-deployment.

civTBI participants sustained a mild to moderate TBI through common non-blast mechanisms, such as motor vehicle accident or sports-related injuries. The head injury must have occurred 1-6 years prior to enrollment.   Duration of LOC and PTA, derived from medical records and self-report, must not have exceeded 24 hours and 7 days, respectively. Participants were excluded if there was an observable intracranial injury on brain imaging (if available). GCS score was between 9 and 15 (if available). As with milTBI participants with multiple head injuries, the most severe served as the "index injury" for estimating time since injury.

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civCON were chosen to control for nonspecific effects of injury on cognitive and brain imaging data. These participants had no history of brain injury or LOC, and no primary blast exposure. Extra-cranial injuries were experienced during the prior 6 years and included ligament damage and fractures of the arms and legs due to sports or motor vehicle accidents.

All prospective participants were excluded if any of the following were present: not fluent in English, history of neurologic disorders associated with cerebral dysfunction and/or cognitive deficit (e.g., cerebral palsy, mental retardation, epilepsy), history of severe psychiatric disorder (e.g., bipolar disorder, schizophrenia) with the exception of post-traumatic stress disorder (PTSD), penetrating gunshot wound to the brain or contraindications to undergoing MRI (e.g., pregnancy, metal implants, claustrophobia). Potential participants were also excluded based on: (1) significant alcohol and/or drug abuse by administration of the Alcohol Use Disorders Identification Test (AUDIT)[28] (cutoff score < 20) and the Drug Abuse Screening Test-10 (DAST-10)[29] (cutoff score < 4); (2) pre-injury psychiatric history based on responses to the Structured Clinical Interview for the DSM-IV Axis-I Disorders (SCID; Overview Module of the Non-Patient Research version November, 2002[30]; and (3) symptom invalidity using a combination of Green's Word Memory Test (WMT)[31] and performance on the neuropsychological test battery.

Self-report measures. The Neurobehavioral Symptom Inventory (NSI)[32] was administered to characterize commonly self-reported symptoms associated with concussion. Severity of PTSD symptoms over the past month was measured with the PTSD Checklist – Civilian version (PCLC)[33]. Self-reported depression symptoms were

assessed with the Center for the Epidemiological Study of Depression Scale (CES-D).[34]

Self report of pain and fatigue were measured using visual analog scales ranging from 0

- 10.

Neuropsychological measures. Participants completed a standard battery of

neuropsychological tests designed to measure cognitive deficits most commonly

associated with mild TBI. The battery included measures of information processing

speed, executive function, and memory: written and oral forms of the Symbol Digit

Modalities Test (SDMT)[35], parts A and B of the Trail Making Test (TMT)[36], Controlled

Oral Word Association Test (COWAT)[37], and the California Verbal Learning Test-2

(CVLT-2).[38]

Stop Signal Task (SST). The SST paradigm used in this study was similar to that

described by Aron and Poldrack[39] and illustrated in Figure 1. The SST consisted of 96

GO (75%) and 32 STOP (25%) trials distributed over 2 imaging runs. On all trials, the

participant was presented with a 500 ms warning stimulus consisting of a central fixation

cross. This was followed by a left or right arrow. For the GO trials, the participant

responded as fast as possible with a left or right key press using the index and middle

fingers of the right hand. For the STOP trials, a red filled box was presented above the

GO (arrow) stimulus. The participant was instructed to attempt to stop his/her response

at the appearance of the red box. The time between the GO (arrows) and STOP (red

box) stimuli is referred to as the stop signal duration (SSD). The number of left and

right arrows was equal; GO and STOP trials and left/right arrows were presented in a

pseudorandom order.

The SSD on STOP trials changed depending on the participant's behavior. If the

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participant inhibited successfully on a STOP trial, then inhibition was made more difficult on a subsequent STOP trial by increasing the SSD by 50 ms; if the participant did not successfully inhibit, then inhibition was made easier by decreasing the SSD by 50 ms. A single staircase was used to ensure sufficient number of both correct and incorrect inhibitions by the end of the task. Average SSD was computed, for each subject, from the values for the last 48 moves of the staircase. The stop signal reaction time (SSRT) was calculated by subtracting the average SSD from the mean of median RT on GO trials.   Higher SSRT values are indicative of poorer inhibition.

The task was programmed using E-Prime software (Psychology Software Tools, Inc., Sharpsburg, PA) and displayed in the scanner using an Avotec back-projection video system (Avotec, Inc., Stuart, FL).

MR Image Acquisition.   Scanning was conducted at the Cleveland Clinic using a Siemens TIM Trio 3T MRI scanner (Erlangen, Germany) equipped with a 12-channel receive-only head array. Whole-brain fMRI scans were acquired with a gradient-echo, echoplanar (EPI) pulse sequence [31 4-mm thick contiguous axial slices, TE=29 ms; TR=2800 ms; flip angle=80°; FOV=256 X 256 mm; matrix=128 X 128; in-plane resolution=2 X 2 mm]. The SST task was performed over two imaging runs each lasting a total of 736 secs (263 volumes per imaging run). High resolution structural MRI (sMRI) scans [T1 with T1-weighted inversion recovery turboflash (MPRAGE), 120 axial slices, thickness 1-1.2mm, Field-of-view (FOV) 256 mm x 256 mm, TI/TE/TR/flip angle (FA) 900ms/1.71ms/1900ms/80, matrix 256x128, receiver bandwidth (BW) 62kH] were acquired for registration with lower resolution EPI images and to measure cortical and subcortical gray and white matter volumes.

Image Analysis (fMRI). The first 4 pre-steady-state volumes of the EPI timeseries were removed. The remaining images were timeshifted, motion corrected, and spatially filtered using a 2D 4mm full width at half maximum (FWHM) Gaussian filter in the Fourier domain. Multiple regression was performed using Analysis of Functional Neuroimaging (AFNI) software [40]. A gamma variate hemodynamic response function (HRF) model used regressors for four trial types: GO correct (GO), GO incorrect, correct inhibition (CI), and incorrect inhibition (II). GO incorrect trials were not subsequently analyzed due to their low frequency (see Results). Individual subject t-maps for GO, CI and II trial types were converted to z-maps and transformed to Talairach stereotaxic space (Talairach and Tournoux, 1988).

Three t-test subtraction maps (CI - GO, II – GO, and II – CI) were generated for each of the 4 groups (milTBI, milCON, civTBI, and civCON). A significant cluster was defined by an individual voxel probability ($p<.005$) and a minimum cluster size (0.684 ml); these joint thresholds set the whole brain false positive rate for a significant cluster equal to $p=0.05$. A disjunction mask was then created for each contrast by combining all suprathreshold voxels from any of the four group t-maps. This produced functional region of interest (fROI) maps for each of the three subtraction conditions. Large fROIs were divided along local minima in the averaged t-maps. Within each fROI and condition, z-statistics were averaged for each subject. For each fROI and subtraction condition, 2 (MIL/CIV) X 2 (TBI/CON) ANOVAs were conducted. False discovery rate (FDR) was used to correct for multiple comparisons. For those fROIs surviving the FDR correction, Tukey B post-hoc analyses were used to identify which groups demonstrated significant differences in the magnitude of the fMRI response.

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Image Analysis (sMRI). All structural MRI scans were reviewed for TBI-related and incidental pathology by a board-certified neuroradiologist (S.E.J.). Quantitative regional brain volumes were obtained using the parcellation method incorporated in Freesurfer 5.1 software[41] using the Desikan atlas.[42] Results for each partcipant were visually inspected by a single rater to ensure accuracy of the cortical surface reconstruction. Manual editing, where necessary, was performed to optimize accuracy. The surface inaccuracies involving skull stripping or frank exclusion of brain parenchyma were edited either by (1) adding control points to aid FreeSurfer in the identification of white matter (since it uses the WM/GM boundary as a starting place for reconstructing the pial surface), (2) by fixing the skull strip by removing remaining dura, or (3) by adding back in the sections of brain that were inadvertently automatically removed. Output included 52 volumes including gray (cortical and subcortical) and white matter regions and total CSF. Correction for intracranial volume (ICV) was achieved by dividing the volume of interest by ICV and multiplying by 100. For each of the 52 volumes, 2 (MIL/CIV) X 2 (TBI/CON) ANOVAs were conducted. FDR was used to correct for multiple comparisons. For those volumes surviving the FDR correction, post-hoc group analyses were performed using the Tukey B statistic.

Results

Of 222 individuals who underwent telephone screening, 107 (48.2%) met screening criteria and were scheduled for study visits. Of those enrolled, 20 participants (7 milTBI, 4 milCON, 2 civTBI, and 7 civCON) were excluded from the final analysis for the following reasons: excessive motion in scanner (n=4), poor cooperation (n=3),

inability to understand test instructions (n=6), claustrophobia in scanner (n=2), incidental

pathology discovered on MRI (n=1), discovery of medical condition on exclusion list

(n=2), and technical problems with SST administration (n=2). The final sample

consisted of 21 milTBI, 22 milCON, 21 civTBI, and 23 civCON participants (Table 1).

There were no significant differences in age or gender between the four groups;

participants were largely male. milTBI participants had significantly fewer years of

education than the other groups. Time since the most severe injury was significantly

longer for milTBI than civTBI participants (Table 1).

For the milTBI group, 5 participants (24% of the sample) had been exposed to a

single blast event, 8 (38%) reported 2 blast exposures, and the remaining 8 (38%)

reported multiple blast exposures (range 3 – 20). For the civTBI group, 6 (29%)

participants had a history of a single concussion, 5 (24%) reported 2 concussions, and 8

(38%) reported multiple concussions (range 3-10; data on additional concussions was

not available for 2 participants in this group).   A chi-square analysis comparing the

civTBI and milTBI groups on the proportion with multiple concussions was not

significant.

Injury relevant data was gathered regarding the most severe TBI experienced.

Twelve milTBI participants reported a loss of consciousness (LOC; 57%) typically

ranging from a few seconds to a few minutes in duration (one subject reported a 2.5

hour LOC) and all subjects reported either PTA or AOC. Within the milTBI group, 18

participants (86%) were labeled as having an injury of mild severity due to LOC of < 30

mins and AOC/PTA of <24 hrs. The other 3 participants (14%) were characterized as

having an injury of moderate severity due in one case to a reported LOC of 2.5 hours

and in 2 cases to a reported AOC/PTA ranging from 5 to 15 days. Within the milTBI group, 13 participants reported suffering additional non-TBI related injuries as a result of the blast episode (polytrauma; 62%).

For the civTBI group, MTBI was caused by participation in sports (13; 62%), motor vehicle accidents (4; 19%), bicycle accident (1; 4.5%), being struck by an object (2; 10%), and by a fall (1; 4.5%). Injury relevant data was gathered regarding the most severe TBI experienced. 8 participants (38%) acknowledged a LOC lasting 1 minute or less in duration. All participants reported PTA or AOC ranging in duration from a few seconds to one hour in 19 participants (mild severity; 90%) and up to a few weeks in 2 participants (moderate severity; 10%). Polytrauma was reported in 6 civTBI participants (29%).

Self-Report Measures. Participants in the milTBI group endorsed significantly more concussion-related symptoms (NSI), PTSD (PCLC), depression (CESD), and pain than did participants in the three remaining groups (Table 1). There were no group differences in self-reported fatigue.

Neuropsychological and SST Performance. Two-way (MIL/CIV vs TBI/CON) ANOVAs were conducted on each neuropsychological and SST index (Table 2). No differences in performance were identified for the main effect of TBI (TBI vs. CON). Relative to the civilian participants, the military sample performed more poorly on neuropsychological testing (oral and written versions of the SDMT, COWAT, and short delay of the CVLT-2). A significant interaction between TBI/CON and MIL/CIV was observed on the long delay of the CVLT-2; posthoc analyses indicated that the milTBI group performed worse than the civTBI group.

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On the SST (Table 2), no significant differences were observed on any of the indices for the main effect of TBI (TBI vs. CON) or for the interaction effect (TBI/CON vs. MIL/CIV). Significant effects were observed on the MIL vs. CIV main effect, with the military groups demonstrating poorer performance than the civilians, characterized by slower reaction times on GO trials, shorter SSD, and longer SSRT.

fMRI. The disjunction analysis identified 25 fROIs for the CI-GO subtraction, 39 for the II-GO subtraction, and 24 for the CI - II subtraction (see Supplementary Figure 1 and Supplementary Tables 1-3). None of the regions had a significant main effect of military service (MIL vs. CIV).

Six regions demonstrated a main effect of TBI (TBI vs. CON): bilateral superior medial frontal gyrus/anterior and middle cingulate gyrus [region #1; Figure 2 and Table 3], left middle frontal gyrus [#2], left middle temporal gyrus [#3], and bilateral precuneus [#4] for the CI-GO subtraction and left amygdala [#12] and left angular gyrus [#13] for the CI-II subtraction (Table 3). For all six regions, the TBI groups demonstrated lower activation than the control groups (Figure 3).

Seven regions demonstrated significant interaction effects: left middle orbital frontal/anterior cingulate gyrus [#5] for the CI-GO subtraction and the right and left inferior temporal gyrus/fusiform gyrus [#6 and #8], right inferior temporal gyrus [#7], left superior temporal gyrus [#9], left caudate [#10], and left cerebellum (Crus II) and cerebellar lobule VIIa/Crus I [#11] for the II-GO subtraction. The pattern of interaction effects (Figure 3) was fairly consistent across all seven regions: the civTBI group exhibited less activation than the civCON group; in contrast, the milTBI group demonstrated more activation than the milCON group.

In light of group differences in education, concussion symptoms (NSI), PTSD (PCLC), depression (CESD), and pain perception (Table 1), we conducted analyses of covariance (ANCOVAs) on each of the 13 significant brain regions. The ANCOVAs were performed with one covariate per analysis rather than with combinations of covariates. None of the covariates (education, NSI, PCLC, CESD, and pain perception) resulted in a significant main or interaction effect becoming non-significant.

sMRI. None of the participants had macroscopic lesions on sMRI scans. None of the 52 FreeSurfer-derived volumes demonstrated significant main or interaction effects after FDR correction.

Correlational Analyses. To identify possible relationships between functional brain activity and neurobehavioral measures, Spearman correlations were performed between the 13 significant fROIs (Table 3) and SST performance (SSD, Go Correct RT), cognitive testing (Trails A, Trails B-A, COWAT), and self-report ratings (PCLC, CESD, Pain, Fatigue and NSI). For the combined TBI groups, two correlations survived an FDR correction for multiple comparisons: left STG correlated significantly with the SDMT (r = -0.61, p < 0.0001) and PCLC (r = 0.54, p = 0.0002). These correlations indicate that greater activation in the left STG in response to Incorrect Inhibitions is associated with poorer performance on a measure of information processing speed (SDMT) and greater self-report of PTSD symptoms (PCLC). No significant correlations were observed for the combined control groups.

Discussion

Results from this fMRI study of inhibitory control processes may be summarized as follows: (1) relative to healthy controls, both blast-related and mechanical TBI

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produce an underactivation when participants correctly inhibit a prepotent response, (2)

when participants are unable to inhibit a response, blast-related and mechanical TBI

demonstrate the opposite neural response, with the former group demonstrating

hyperactivation and the latter hypoactivation relative to controls, (3) these results could

not be explained by SST performance, neuropsychological test results, demographic

variables, or self-reported symptoms, including a measure of PTSD, and (4) SST-

related activity during failed inhibition in the left STG is correlated with poorer

performance on a measure of information processing speed and greater PTSD-related

complaints in the TBI group. These findings are the first to demonstrate a neural basis

for distinguishing blast-related from mechanical TBI in humans. More broadly, our fMRI

results are noteworthy for identifying a "neural signature" associated with TBI up to six

years post injury in the absence of demonstrable cognitive deficits.

When participants correctly inhibit their responses on the SST (CI - GO and CI -

II; Figure 3), TBI participants, regardless of etiology, demonstrate hypoactivation in

bilateral medial prefrontal, bilateral precuneus, and left inferior parietal regions. These

frontal and parietal regions are frequently associated with the default mode network

(DMN), a neural system active during the resting state[43] and closely linked with

semantic systems involved in reasoning, planning and problem solving.[44] Using an

independent component analysis of the SST in healthy individuals, Zhang & Li[45] noted

that activity in DMN regions (ventromedial prefrontal cortex, posterior

cingulate/precuneus, and inferior parietal) correlates with inhibitory accuracy on the SST.

Bonnelle et al.[29] also found differences in activation within DMN brain regions

(precuneus, posterior cingulate cortex) between civilian TBI participants and healthy

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==controls during performance of the SST. Our results, therefore, suggest that TBI alters==
==DMN activity during successful inhibitory processing.==

Successful inhibition was also associated with decreased activation of the left amygdala in both TBI groups. Damage to the amygdala has been consistently linked with emotional sequelae of TBI in both military[46, 47] and civilian[48] settings. The location of the structure in the anterior temporal lobe makes it particularly vulnerable to injury.[49] The decreased amygdalar activation during inhibition in TBI participants suggests that emotional salience may play a less prominent role in inhibitory processes for these participants than for non-TBI controls. This is in contrast to studies of individuals with PTSD[50, 51], where the opposite pattern is observed (i.e., hyperactivation of the amygdala).

In contrast to successful inhibitions where both TBI groups demonstrated hypoactivation relative to controls, clear differences were observed between blast-related and mechanical TBI groups during unsuccessful inhibition (II-GO subtraction) in the left caudate nucleus and left posterior lobe of the cerebellum. As shown in Figure 3, the blast-related TBI group demonstrated hyperactivation in these regions relative to the military controls, whereas the mechanical TBI group showed hypoactivation relative to the civilian controls. It is noteworthy that the caudate demonstrates increased activity during feedback processing.[52] The posterior lobe of the cerebellum, in particular the hemispheric parts of lobule VIIA (Crus I and Crus II) and lobule VIIB, has multiple cognitive and emotional functions, with focal lesions resulting in impairments in executive functions, spatial cognition, language, and affect.[53] We speculate that blast-related TBI may heighten activation of brain regions that are associated with the

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cognitive/emotional interpretation of negative feedback. In contrast, mechanical TBI

results in a reduction in these same brain regions.

Incorrect Inhibitions elicited increased activation in the milTBI group relative to all

other groups in bilateral inferior temporal and fusiform gyri. These regions are thought to

be involved in the attentional modulation of visual engagement.[54, 55] Attentional

modulation is crucial to responding to visual cues (e.g., stop signal) by filtering out goal

irrelevant information quickly to successfully inhibit responses.[55] Our findings suggest

that milTBI individuals may receive decreased input from orbital frontal regions on

inhibition trials, contributing to inefficient compensatory overactivation of temporal

regions in attending to stop cues. Hyperactivation in inferior temporal regions in the

milTBI participants may be associated with difficulty in appropriately integrating,

contextualizing, and responding to the ttop signal cue.

Individuals with blast-related TBI are more likely to express non-specific

complaints of difficulties with executive functioning and affective disturbances than

individuals who experience TBI in civilian life.[56] Indeed, our milTBI participants endorsed

significantly more symptoms of PTSD, depression, pain, and postconcussion syndrome.

Our brain activation results, however, remained significant even after controlling for self-

reported symptoms. Our results do not support the view that self-reported symptoms,

like PTSD, provide the most salient explanation for TBI cognitive symptoms.[1, 57, 58]

Furthermore, we have demonstrated a distinction in fMRI activation patterns between

blast-related and mechanical TBI that appears to be independent of the presence of

PTSD.

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. Possible pathophysiological bases underlying our finding that task-activated fMRI discriminates blast-related from mechanical TBI may be related to recent results of a diffusion tensor imaging (DTI) study. Davenport et al.[59] found lower fractional anisotropy (FA) in white matter in blast-related military TBI compared to Veterans who had previously incurred mechanical TBI as civilians. Moreover, FA was more affected in persons with multiple blast-related exposures. We speculate that the greater disruption of white matter integrity in blast-related TBI produces a greater alteration in the activation of brain networks subserving response inhibition than in mechanical TBI.

It is important to note that we did not observe group differences in two brain regions that are traditionally associated with response inhibition. fMRI and lesion studies highlight the role of the preSMA and right inferior frontal cortex/insula in response inhibition.[39, 45, 60, 61] While these brain regions were activated by the SST (see Supplementary Figure 1), no significant group differences were observed in these two regions. In contrast, our finding of reduced activation among TBI participants in the default mode network during correct inhibitions may be consistent with other findings of decreased resting state default mode connectivity in individuals with TBI.[62, 63]

Individuals in both TBI groups demonstrated poorer inhibition (slower reaction times on GO trials, shorter SSD, and longer SSRT) than control participants. The clinical implications of poor performance on measures of response inhibition require further study. It is unclear whether poor performance is associated with impulsive decision making with poor judgment, increased driving accidents, aggressive and/or unlawful behavior, and substance use/abuse. In the military theater, impaired response inhibition may even be associated with decreased survival rates. Interestingly,

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correlational analyses showed that activation in one brain region, the left STG, was associated with failed inhibition and increased PTSD symptoms in TBI patients. The precise meaning of this relationship is difficult to discern since no other relationships were observed between brain activity and neurobehavioral measures,

Relative to other fMRI studies in TBI, our sample size is large. In addition, the four group composition allowed us not only to compare TBI with controls, but also blast-related with mechanical TBI. It is also the first study to examine the inhibitory control circuits disrupted by blast-related TBI. This study is not without limitations, however. First, it is important to note that what we are calling a blast-related TBI is more likely a combination of pressurization changes associated with blast plus secondary and tertiary mechanical forces. In effect, we are comparing blast+mechanical versus mechanical TBI, since in all likelihood pure blast-related injuries occur rarely in the combat theater. Second, the SST is designed to achieve approximately 50% correct inhibitions. Although our task achieved somewhat less than 40% correct inhibitions, we had enough trials (n>12) to successfully generate brain maps for the CI condition. Third, the diagnosis of blast-related TBI is based on self-report, since military personnel who experience a mild to moderate TBI are rarely removed from the combat theater and medical records are minimally recorded. Fourth, despite our best attempts to equate the four groups based on demographic variables, the milTBI group was less educated than the two civilian groups. When education was used as a covariate, the fMRI findings remained significant. Fifth, we did not observe differences between TBI and control groups on SST performance and neuropsychological testing. The absence of a TBI effect is likely attributable to the reduced sensitivity of cognitive measures to

mild/moderate TBI during the chronic post-injury period. Sixth, the time since injury was

significantly shorter in the mechanical (29.7 months) than blast-related (52.9 months)

TBI groups. Both groups, however, were clearly in the chronic stage post-injury.

Furthermore, when this variable served as a covariate, it did not influence the fMRI

results. Seventh, we would have preferred to recruit milCON participants who had

experienced an orthopedic injury to equate with the civCON group. This proved to be

difficult to recruit since most orthopedic injuries occurred in the context of blast

exposure. Finally, although our two TBI groups had a comparable proportion of single

vs. multiple concussions, the sample size of our study is underpowered to properly

evaluate this variable in the context of our behavioral and imaging data.

To conclude, we found common and distinct patterns of brain activation in blast-

related and mechanical TBI. During correct inhibitions, both TBI groups demonstrated

decreased activation in the DMN. In contrast, during failed inhibition trials, blast-related

TBI exhibited hyperactivation and mechanical TBI produced hypoactivation. These

divergent brain activation patterns were independent of self-reported complaints,

including PTSD. The identification of an imaging test that is specifically sensitive to

blast-related TBI in humans raises numerous clinical possibilities. It is conceivable that

our brain activation patterns in response to an inhibitory control task could be used as a

basis for the diagnosis of blast-related TBI in the clinical setting. The efficacy of

potential treatments for the sequelae of blast-related TBI could also be measured with

this imaging biomarker. This is critical since neuropsychological testing is relatively

insensitive to the chronic effects of blast-related MTBI. Finally, these findings suggest

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possibilities for developing an animal model for testing the effects of blast-related

trauma on neural function based on inhibitory control testing.

Conflicts of Interest: No competing financial interests exist.

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Figure Legends

Figure 1. Schematic timeline for the Stop Signal Task (see Methods for details).

Figure 2. fROIs (shown in color) demonstrating significant main or interaction

effects for the CI – GO, II – GO, and CI - II subtractions. Numbers correspond with

brain region described in Table 3 and Figure 3. CI = correct inhibition, II = incorrect

inhibition, GO = go conditions. Background gray-scale brain images derived from a

rendering of the gray-white matter surface using Caret software (Washington University,

St. Louis).

Figure 3. Bar graphs illustrating significant main and interaction effects for the CI

– GO, II – GO, and CI - II subtractions. CI = correct inhibition, II = incorrect inhibition,

GO = go trial conditions. Numbers in brackets correspond to brain regions shown in

Figure 2 and described in Table 3. Note that regions 1-5 are from the CI – GO

subtraction, regions 6-11 from the II – GO subtraction, and regions 12-13 are from the

CI - II subtraction. Error bars = s.e.m.

Supplementary Figure 1. fROIs derived from the CI – GO (N=25), II – GO

(N=39), and CI - II (N=24) subtractions. CI = correct inhibition, II = incorrect inhibition,

GO = go trial conditions. Colors are used to demarcate distinct fROIs and have no

interpretive significance. Background gray-scale brain images derived from a rendering

of the gray-white matter surface using Caret software (Washington University, St. Louis).

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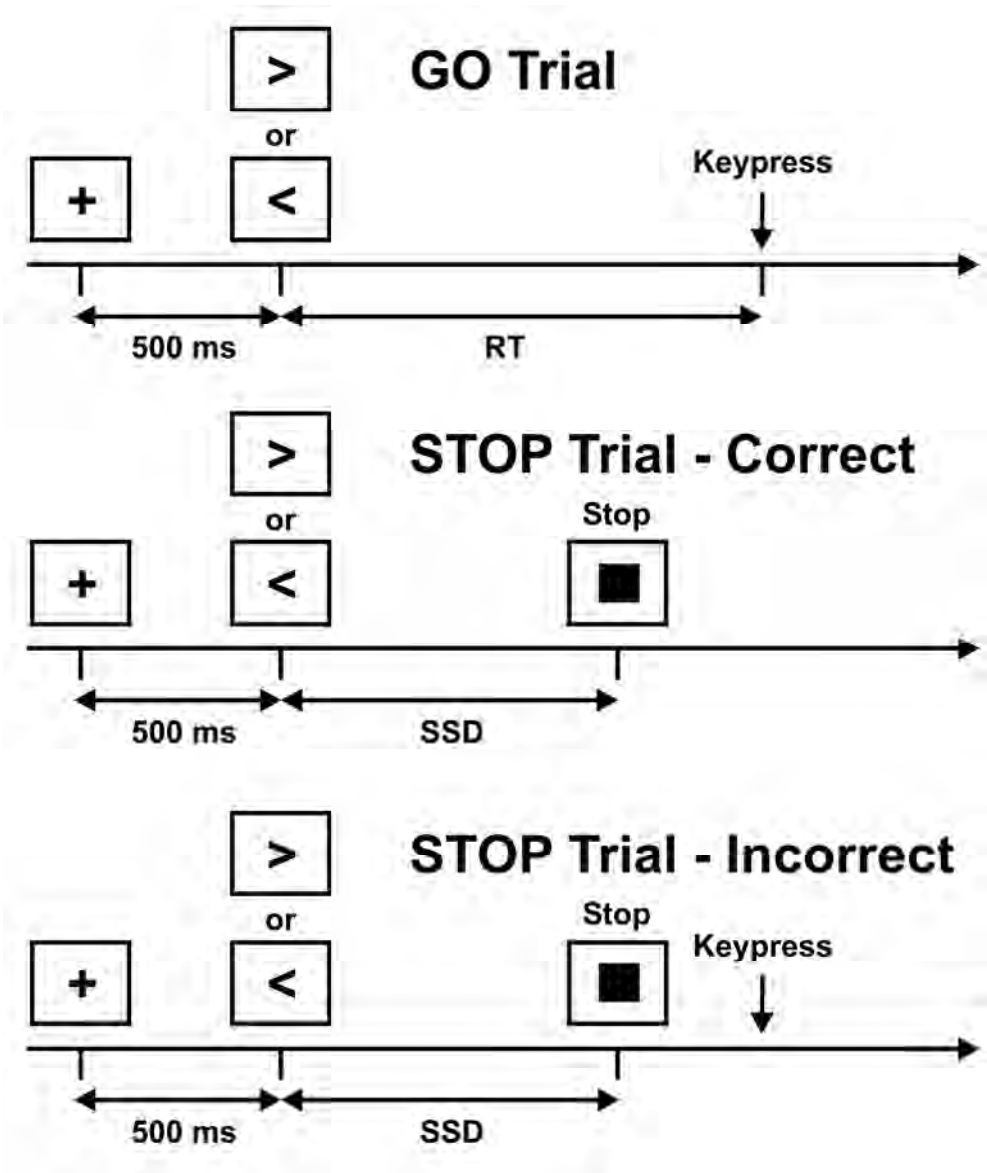
Figure 1
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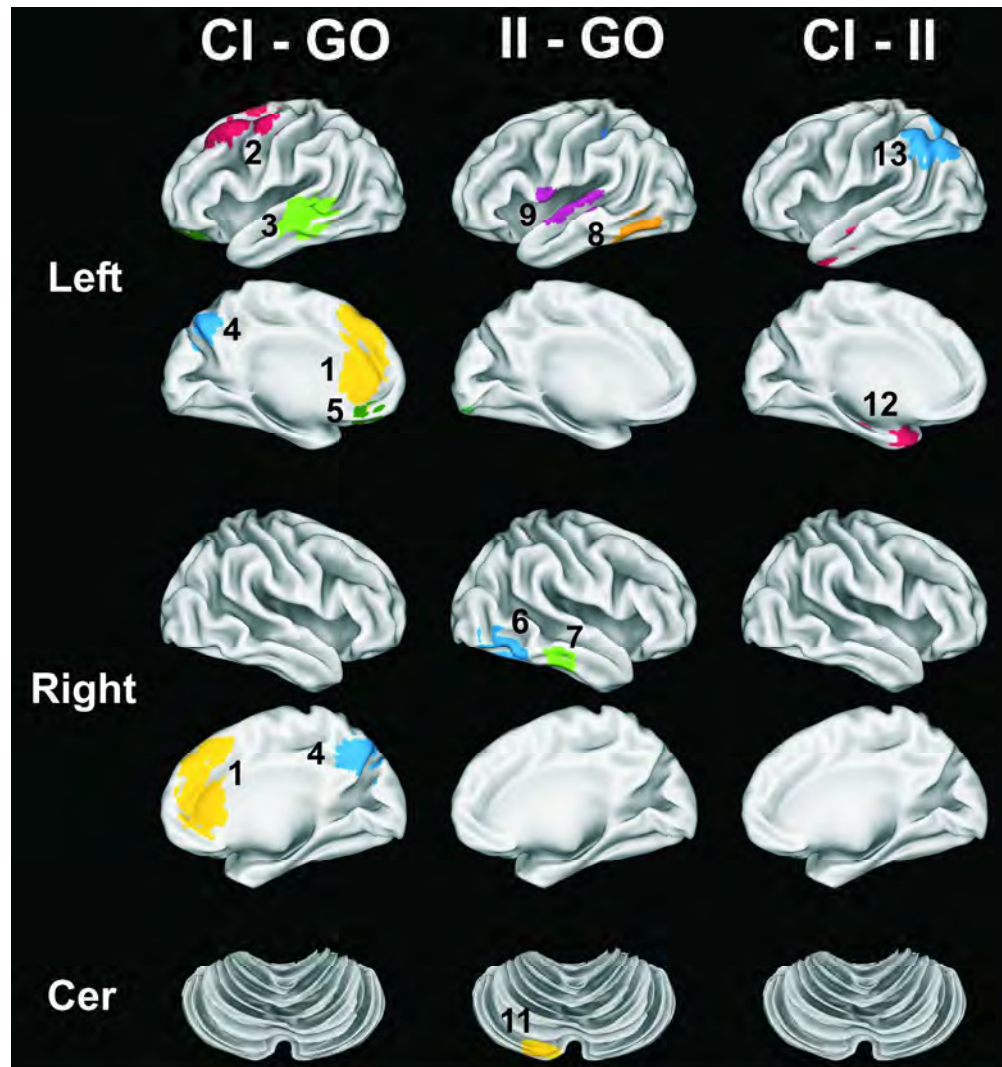
Figure 2
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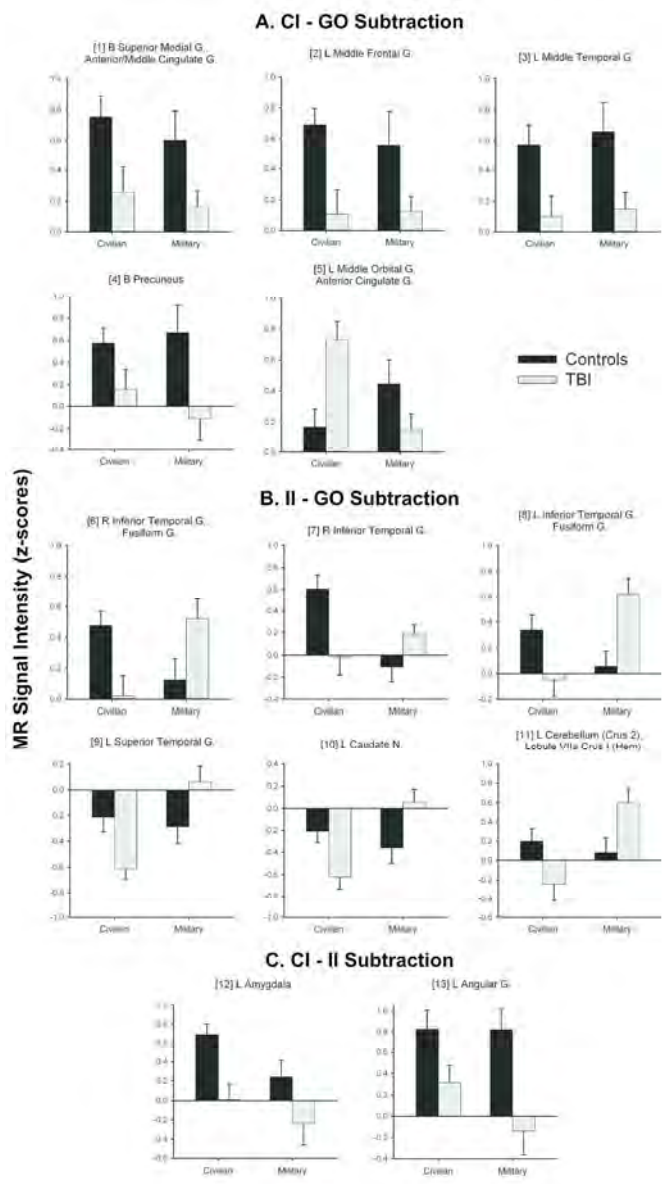
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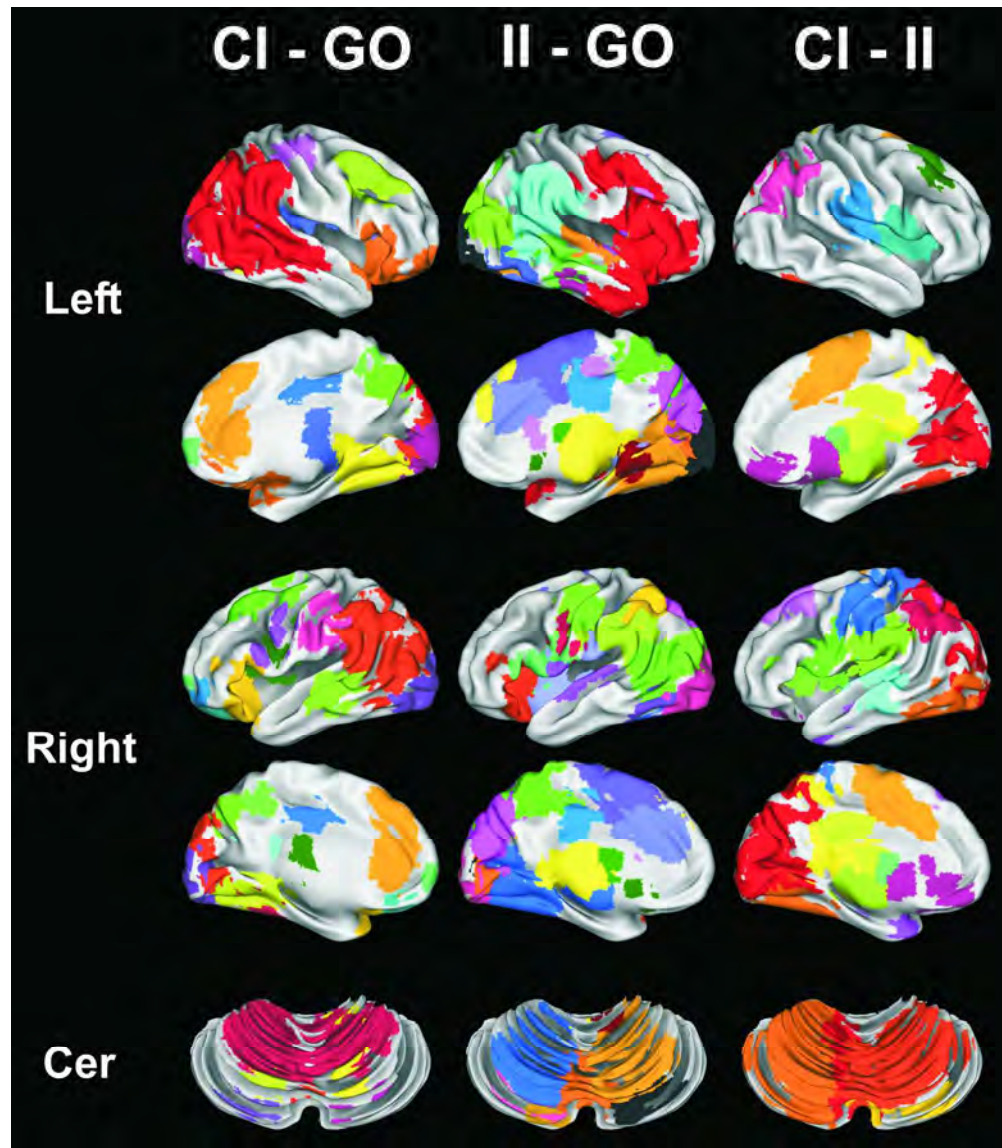
Supplementary Figure 1
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Table 1. Demographic Information, TBI Injury Data, and Self-Report Ratings

Variable	milTBI (n = 21)	milCON (n = 22)	civTBI (n = 21)	civCON (n = 23)	2 X 2 ANOVA		
					TBI vs. CON	Mil vs. Civ	Interaction
Age - yrs	28.3 (4.6)*	29.7 (5.6)	26.2 (4.8)	27.3 (4.5)	-	0.033 (mil>civ)	-
Education - yrs	12.7 (1.3)	14.1 (2.2)	15.1 (1.8)	15.5 (2.4)	0.040(TBI<CON)	<0.001(mil<civ)	-
Sex - number (%) female	1 (4.7)	1 (4.5)	2 (9.5)	0 (0)	-	-	-
Handedness - number (%) right	18 (86)	22 (100)	20 (95)	20 (87)	-	-	-
Months since last TBI	52.9 (17.9)	NA	29.7 (16.1)	NA	-	-	-
Number (%) with >1 primary blast	16 (76.2)	NA	NA	NA	-	-	-
PCLC - total	53.8 (15.6)	24.9 (10.3)	24.7 (5.4)	25.0 (10.6)	<0.001(TBI>CON)	<0.001(mil>civ)	<0.001(milTBI > milCON, civTBI, civCON)
CESD - total	22.0 (12.1)	7.4 (9.3)	7.3 (7)	7.5 (7.2)	<0.001(TBI>CON)	<0.001(mil>civ)	<0.001(milTBI > milCON, civTBI, civCON)
Pain - total	3.1 (2.5)	0.6 (1.3)	0.9 (1.5)	0.6 (1.4)	<0.001(TBI>CON)	0.007 (mil>civ)	0.003 (milTBI > milCON, civTBI, civCON)
Fatigue - total	4.1 (2.9)	2.2 (2.4)	2.4 (2.0)	2.8 (2.2)	-	-	-
NSI - total	33.1 (12.7)	7.9 (9.6)	10.5 (7.8)	8.4 (8.8)	<0.001(TBI>CON)	<0.001(mil>civ)	<0.001(milTBI > milCON, civTBI, civCON)

* Mean (SD), - = not significant.

TBI = traumatic brain injury, CON = controls, mil = military, civ = civilian, PCLC = PTSD Checklist - Civilian Version,

CESD = Center for the Epidemiological Study of Depression Scale, NSI = Neurobehavioral Symptom Inventory.

Table 2. Neuropsychological Testing and Stop Signal Task Performance

Variable	milTBI	milCON	civTBI	civCON	TBI vs CON	Mil vs Civ	Interaction
						2 x 2 ANOVA	
Neuropsychological Testing							
Trails A - sec	26.5 (10.5)*	23.9 (4.6)	22.0 (7.2)	23.0 (9.7)	-	-	-
Trails B - sec	65.5 (41.1)	60.6 (26.8)	50.6 (20.0)	59.0 (28.9)	-	-	-
Trails B-A - sec	39.0 (34.2)	36.6 (24.5)	28.5 (19.1)	35.9 (25.4)	-	-	-
COWAT - total	36.9 (9.5)	36.9 (9.0)	43.6 (9.8)	43.6 (15.0)	-	0.007** (Mil < Civ)	-
CVLT Short Delay - total	9.6 (3.4)	10.2 (3.1)	11.6 (1.7)	10.7 (2.2)	-	0.030 (Mil < Civ)	-
CVLT Long Delay - total	9.4 (3.9)	10.8 (3.1)	12.0 (1.7)	10.6 (2.3)	-	-	0.041***
CVLT - T-score	50.4 (7.9)	49.6 (8.9)	52.2 (7.7)	52.5 (6.4)	-	-	-
SDMT - total written correct	51.5 (12.5)	58.2 (8.7)	61.8 (15.1)	61.2 (9.6)	-	0.010 (Mil < Civ)	-
SDMT - total oral correct	61.2 (13.7)	66.0 (11.1)	68.8 (16.3)	71.9 (12.1)	-	0.024 (Mil < Civ)	-
Stop Signal Task							
GO Correct - % correct	88.8 (7.3)	91.9 (6.3)	87.8 (8.7)	90.0 (6.7)	-	-	-
GO Correct - median RT (ms)	650.4 (84.7)	683.5 (77.7)	715.9 (64.9)	706.6 (94.2)	-	0.014(Mil < Civ)	-
STOP Correct - % correct	37.1 (4.8)	37.5 (4.8)	37.9 (4.6)	38.3 (4.6)	-	-	-
SSD - ms	499.8 (124.9)	545.3 (103.3)	596.0 (93.2)	607.9 (91.6)	-	0.0006 (Mil < Civ)	-
SSRT - ms	150.6 (85.3)	138.0 (59.4)	119.6 (58.2)	98.5 (77.9)	-	0.023 (Mil > Civ)	-

* Mean (SD), ** p-value, *** milTBI < civTBI (pairwise posthoc analysis), - = not significant.

TBI = traumatic brain injury, CON = controls, mil = military, civ = civilian, COWAT = Controlled Oral Word Association Test, CVLT = California Verbal Learning Test, SDMT = Symbol Digit Modalities Test, SSD = Stop Signal Duration, SSRT = Stop Signal Reaction Time

Table 3. Significant Functional ROIs from 2 (Mil / Civ) x 2 (TBI / CON) ANOVA

#		Region	BA	x	y	z	Vol. (ml)	TBI vs. CON	Mil vs. Civ	Interaction
CI - GO Subtraction										
1	B	Superior Medial G., Anterior/Middle Cingulate G.	8, 9, 32	0.5	34.8	27.8	10.22	*	-	-
2	L	Middle Frontal G.	6,8	-35.2	10.4	50.2	2.49	*	-	-
3	L	Middle Temporal G.	21	-57.7	-31.6	-2.9	2.81	*	-	-
4	B	Precuneus	7	6.7	-64.0	37.9	2.74	*	-	-
5	L	Middle Orbital G., Anterior Cingulate G.	11	-15.2	41.3	-9.3	1.22	-	-	*
II - GO Subtraction										
6	R	Inferior Temporal G., Fusiform G.	37	48.9	-57.1	-15.2	2.07	-	-	*
7	R	Inferior Temporal G.	20	58.4	-26.0	-18.7	0.52	-	-	*
8	L	Inferior Temporal G., Fusiform G.	37	-50.8	-59.3	-16.3	1.10	-	-	*
9	L	Superior Temporal G.	22	-57.6	-12.9	3.5	1.00	-	-	*
10	L	Caudate N.	-	-21.7	-15.0	29.1	1.72	-	-	*
11	L	Cerebellum (Crus 2), Lobule Vlla Crus I (Hem)	-	-11.9	-83.9	-22.5	0.16	-	-	*
CI - II Subtraction										
12	L	Amygdala	-	-30.2	0.1	-21.3	1.89	*	-	-
13	L	Angular G.	39, 40	-43.3	-58.2	40.7	4.77	*	-	-

Column header note: "2 X 2 ANOVA" spans TBI vs. CON, Mil vs. Civ, Interaction.

* Significant main or interaction effect, - = not significant.

TBI = traumatic brain injury, CON = controls, mil = military, civ = civilian, R = right, L = left, B = bilateral, G. = gyrus.

Supplementary Table 1. Correct Inhibitions - GO

Side	Region	BA	x	y	z	Vol. (ml)
	Positive ROIs					
R	Angular G., Inf. ParietalL., Mid. Temporal & Occip. G.	7, 19, 21, 22, 37, 39, 40	47.3	-52.2	18.8	38.43
L	Mid. Occipital G., Mid. Temporal G., Angular G.	7, 19, 37, 39	-37.5	-62.2	23.6	22.71
R	Insula L., Inf. Frontal G. (p. Orbitalis)	44, 45	33.0	24.4	-4.7	12.30
B	Sup. Medial G., Ant. Cingulate C.	8, 9, 32	0.5	34.8	27.8	10.22
L	Insula L., Inf. Frontal G. (p. Orbitalis)	44, 45	-34.3	19.5	-2.5	8.91
R	Lingual, Fusiform G.	19, 37	22.3	-51.0	-6.0	5.24
L	Lingual, Fusiform G.	19, 37	-19.9	-54.8	-6.0	3.88
R	Mid. Frontal G.	6, 8	38.9	14.3	41.5	3.76
L	Mid. Temporal G.	21	-57.7	-31.6	-2.9	2.81
R	Precuneus	7	6.7	-64.0	37.9	2.74
L	Mid. Frontal G.	6, 8	-35.2	10.4	50.2	2.49
L	Precuneus	5	-3.0	-47.5	44.1	1.32
L	Sup. Medial G., Mid. Orbital G.	10	-4.1	60.3	6.4	1.26
L	Mid. Orbital G.	11	-15.2	41.3	-9.3	1.22
L	Mid. Orbital G.	11	-37.7	50.1	-1.0	0.84
B	Mid. Cingulate C.	23	-0.4	-18.4	36.7	0.82
	Negative ROIs					
L	Inf. & Mid. Occipital, Calcarine G.	17, 18	-19.9	-87.1	-4.1	12.00
R	Inf. & Mid. Occipital, Calcarine G.	17, 18	20.2	-86.9	-0.7	8.62
B	Cerebellar Vermis (4/5)	-	-1.4	-50.2	-17.7	7.43
L	Putamen	-	-23.2	-10.7	15.7	7.09
R	Thalamus	-	22.8	-13.6	14.3	5.57
L	SupraMarginal G., Postcentral G.	1, 2, 3, 40	-46.8	-24.6	31.8	2.74
R	Postcentral G., Precentral G.	4	34.9	-24.0	50.8	1.57
L	Tapetum	-	-20.4	-43.8	25.1	1.35
L	Precentral G.	6	-56.0	2.6	27.4	1.18

Supplementary Table 2. Incorrect Inhibitions - GO

Side	Region	BA	x	y	z	Vol. (ml)

Positive ROIs

Side	Region	BA	x	y	z	Vol. (ml)
R	Right Inf. Frontal G, Insula, Precentral G, Temporal Pole	6, 13, 38, 44, 45	43.2	12.4	6.9	36.99
L	Cuneus, Precuneus, Sup. Parietal Lobule	7, 17, 18, 19	-4.4	-71.7	29.5	21.99
R	Supramarg. G., Angular G., Sup. & Mid. Temporal G.	37, 39, 40	53.7	-44.2	19.3	17.57
L	Lingual G., Fusiform G., Calcalrine	19,37	-17.0	-51.3	-5.1	16.81
R	Lingual G., Fusiform G., Calcalrine	19,37	18.5	-57.5	-1.8	14.95
B	Ant. & Mid. Cingulate G.	24, 32	0.7	20.8	33.7	14.46
B	SMA	6	1.2	2.8	56.8	13.73
L	Insula Lobe, Inf. Frontal G.	13, 44, 45	-35.3	17.2	4.3	12.72
R	Thalamus	-	3.2	-20.7	5.8	10.46
B	Cerebellar Vermis (6)	-	0.0	-72.8	-3.9	10.06
L	SupraMarginal G. IPC	40	-53.0	-41.0	27.2	8.83
L	Precuneus	5, 7	-2.4	-47.9	51.8	7.31
R	Mid. & Sup. Occipital G.	19	37.4	-71.6	15.7	6.39
L	Mid. Occipital G.	19, 39	-31.5	-76.8	16.5	6.07
L	Mid. Temporal G.	19, 39	-48.1	-58.0	6.5	6.07
R	Mid. Temporal G.	21	51.7	-28.8	-5.7	4.16
L	Rolandic Operculum, Precentral G.	44	-52.0	4.5	12.3	3.05
L	Postcentral, Precentral G.	4, 6	-42.3	-13.5	42.8	2.44
L	Inf. Parietal Lobule	7	-35.6	-50.4	42.1	2.42
L	Insula L.	13	-40.0	-9.7	5.1	2.19
R	Inf. Temporal, Fusiform G.	37	48.9	-57.1	-15.2	2.07
L	Caudate N.	-	-12.0	2.6	11.1	1.72
B	Mid. Cingulate C.	23, 31	0.2	-21.0	35.9	1.70
L	Inf. Temporal G., Inf. Occip. G.	19	-50.8	-59.3	-16.3	1.10
R	ParaHippocampal G.	-	19.3	-40.4	-3.3	1.07
R	Caudate N.	-	12.2	2.5	13.0	0.89
R	Inf. Temporal G.	20	58.4	-26.0	-18.7	0.52
R	Sup. Parietal L.	7	22.8	-61.3	40.4	0.46
B	Sup. Medial G.	9	4.3	41.7	40.1	0.39
L	Precentral G.	4, 6	-49.0	-8.7	25.4	0.28
L	Cerebellum (Crus 2), Lobule VIIa Crus I (Hem)	-	-11.9	-83.9	-22.5	0.16

Negative ROIs

L	Inf. & Mid. Occipital, Calcarine G.	17, 18	-22.3	-85.9	-3.6	12.98
R	Inf. & Mid. Occipital, Calcarine G.	17, 18	22.9	-86.9	-2.1	11.79
R	Caudate N.	-	19.7	5.7	23.3	4.68
L	Caudate N.	-	-21.7	-15.0	29.1	1.72
R	Sup. Temporal G.	22	57.5	-11.1	6.1	1.15
L	Sup. Temporal G.	22	-57.6	-12.9	3.5	1.00
R	Hippocampus	-	28.3	-37.0	8.7	0.81
L	Caudate N.	-	-12.3	19.9	0.9	0.78

Supplementary Table 3. Incorrect Inhibitions - Correct Inhibitions

Side	Region	BA	x	y	z	Vol. (ml)
Positive ROIs						
L	Cuneus, Precuneus, Calcarine, Lingual G.	7,17,18	-6.2	-68.6	13.0	45.19
B	SMA	6	0.6	-0.2	49.8	11.74
L	Cerebellum (VI)	-	-29.9	-57.8	-17.3	10.89
L	Thalamus	-	-8.3	-23.2	15.1	9.26
R	Thalamus	-	10.2	-18.8	12.4	8.73
L	SupraMarginal G.	40	-48.8	-26.4	21.3	7.48
R	Cerebellum (VI)	-	18.3	-58.8	-14.9	6.12
L	Postcentral G.	3	-36.1	-22.5	46.4	5.62
R	Insula Lobe	13	40.4	6.8	10.7	4.89
R	Rolandic Operculum, Supramarginal G.	40,13	46.0	-22.8	19.1	4.78
L	Thalamus	-	0.8	-22.2	-3.8	3.97
L	Rolandic Operculum	13	-46.0	-1.4	15.4	3.06
L	Insula Lobe	13	-33.5	16.7	12.1	2.17
L	Pallidum	-	-12.4	-0.1	7.7	1.70
R	Pallidum	-	16.0	0.3	6.7	1.42
R	Cerebellum (VIII)	-	15.8	-73.3	-30.3	1.13
L	Sup. Parietal Lobule	5, 7	-19.4	-44.5	60.3	0.50
Negative ROIs						
B	Caudate, Ant. Cing., Orbital, Rectal G	11, 12, 25, 32	-0.1	25.8	-3.0	6.22
L	Angular G., Inf. Par.	39, 40	-43.3	-58.2	40.7	4.77
R	Angular G., Inf. Par.	39, 40	44.5	-60.8	37.4	4.03
L	Sup., Mid. Frontal G.	8	-23.1	22.3	49.9	3.35
L	Mid. Temporal G.	21	-60.0	-28.7	-2.2	2.15
L	Amygdala	-	-30.2	0.1	-21.3	1.89
R	Mid. Frontal G.	8	29.1	22.5	47.8	1.25